Supporting Information

An Orally Available BACE1 Inhibitor that Affords Robust CNS Aβ Reduction without Cardiovascular Liabilities

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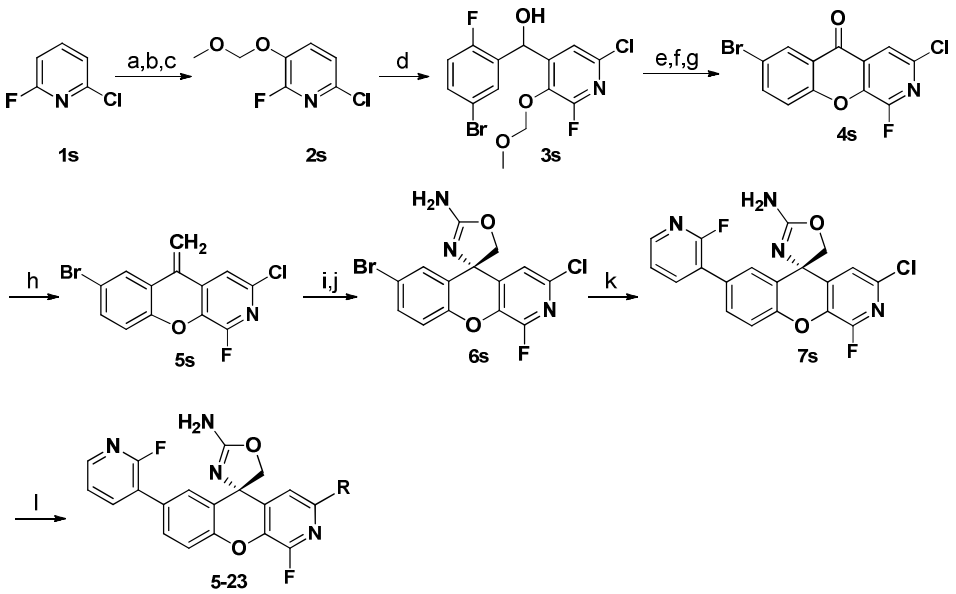
Synthesis of 3-Aza-4-fluoroxanthene Analogues

The preparation of the 3-aza-4-fluoroxanthene analogues is outlined in Scheme 1. The synthesis started with the installation of a MOM-protected alcohol at the 5-position of 2-chloro-6-fluoropyridine (**1s**). The resulting ether **2s** was lithiated at the 3-position using LDA and quenched with 5-bromo-2-fluorobenzaldehyde to afford the racemic alcohol **3s**. Oxidation of the resulting alcohol to the corresponding ketone followed by removal of the MOM group and cyclization under basic conditions gave the azaxanthone intermediate **4s**. As described previously,[12] the racemic aminooxazoline unit was installed by olefination of the ketone and

Scheme 1. Synthesis of 3-aza-4-fluoroxanthenes[a]



[a]Reagents and conditions: (a) lithium diisopropylamide, THF, $B(OiPr)_3$, 0 °C; (b) NaOH, H_2O_2, H_2O; (c) chloromethyl methyl ether, K_2CO_3, acetone, 60 °C, 69% yield three steps; (d) lithium diisopropylamide, THF, - 78 °C, 5-bromo-2-fluorobenzaldehyde, 57% yield; (e) tetrapropylammonium perruthenate, NMO. (f) BBr_3, DCM; (g) $CaCO_3$, dioxane, reflux, 69% yield three steps; (h) MeMgBr, THF, 0 °C, 66% yield; (i) AgOCN, I_2, THF, 0 °C, then NH_3. (j) Chiral HPLC separation, 40% yield two steps; (k) (2-fluoropyridin-3-yl)boronic acid, Amphos, K_3PO_4, dioxane/water (3:1), 80 °C, 67% yield; (l) R-boronic acid or boronic ester, Amphos, K_3PO_4, dioxane/water (3:1), 100 °C, or RR'NH, X-Phos palladium precatalyst, lithium bis(trimethylsilyl)amide, THF.

subsequent addition of in situ generated iodine isocyanate to the olefin **5s** followed by treatment with ammonia. Chiral separation of the racemate using supercritical fluid chromatography (SFC) gave the desired enatiomerically pure key intermediate **6s**. A selective Suzuki-Miyaura

cross-coupling of the bromide with (2-fluoropyridin-3-yl)boronic acid, the optimal P3 group based on the previous SAR results[19,20] provided **7s** which was subjected to a second cross-coupling reaction with appropriate P2' groups to yield the desired 3-aza-4-fluoro-xanthene analogues **5-23**.

Experimental Section

BACE1 enzymatic assay. BACE1 enzymatic activity was determined by the enhancement of fluorescence intensity upon enzymatic cleavage of the fluorescence resonance energy transfer substrate. The BACE1 recognition and cleavage sequence of the substrate is derived from the reported literature,[i] and the fluorophore and quencher dyes are attached to side chain of Lys residues at the termini of the substrate peptide. The human recombinant BACE1[ii] assay was performed in 50 mM acetate, pH 4.5/8% DMSO/100 μM Genepol/0.002% Brij-35. In dose-response IC_{50} assays, 10 point 1:3 serial dilutions of compound in DMSO were pre-incubated with the enzyme for 60 min at room temperature. Subsequently, the substrate was added to initiate the reaction. After 60 min at room temperature, the reaction was stopped by addition of 0.1 M Tris base to raise the pH above the enzyme active range, and the increase of fluorescence intensity was measured on Safire II microplate reader (Tecan, Männedorf, Switzerland). IC50 values were averaged values determined by at least two independent experiments. The standard deviation and the number of experiments for each compounds are listed in Table 1s.

Table 1s. Standard Deviation of BACE1 Enzymatic Assay and Cell-based Assay.

Cpd	IC_{50} (μM)[a]	
	BACE1	Cell[b]
1	0.0022 ± 0.0078, n = 361	0.025 ± 0.0078, n = 55
3	0.0009 ± 1.47E-4, n = 23	0.021 ± 0.010, n = 8
4	0.0003 ± 1.1E-4, n = 19	0.0041 ± 0.0019, n = 8
5	0.0007 ± 9.15E-4, n = 5	0.008 ± 0.0013, n = 3
6	0.0003 ± 5.3E-5, n = 8	0.0033 ± 0.0016, n = 6
7	0.0004 ± 0.0, n = 2	0.006 ± 0.0015, n = 2
8	0.0004 ± 5.73E-5, n = 2	0.006 ± 0.0024, n = 2
9	0.0008 ± 1.51E-4, n = 3	0.012 ± 2.39 E-4, n = 2
10	0.0012 ± 2.53E-4, n = 5	0.026 ± 0.0056, n = 3
11	0.0003 ± 1.91E-5, n = 2	0.019 ± 0.021, n = 2
12	0.0004 ± 4.95E-6, n = 2	0.0065 ± 0.0023, n = 2
13	0.0002 ± 7.78E-6, n = 2	0.0034 ± 1.6E-4, n = 2
14	0.0004 ± 2.83E-6, n = 2	0.0048 ± 0.001, n = 2
15	0.0003 ± 7.26E-5, n = 14	0.004 ± 0.0017, n = 6
16	0.0003 ± 1.07E-4, n = 12	0.004 ± 0.0022, n = 5
17	0.001 ± 4.67E-5, n =2	0.105, n = 1
18	0.0007 ± 2.47E-4, n = 8	0.019 ± 0.019, n = 4
19	0.0003 ± 9.26E-5, n = 7	0.005 ± 0.002. n = 4
20	0.0003 ± 1.64E-4, n = 9	0.006 ± 0.0048, n = 6
21	0.0002 ± 9.52E-5, n = 9	0.004 ± 0.0013, n = 5
22	0.0002 ± 7.07E-5, n = 2	0.003 ± 0.0026, n = 4
23	0.0003 ± 1.15E-4, n = 2	0.023 ± 0.011, n = 2

Cell-based assay. Human embryonic kidney cells (HEK293) stably expressing APP_{SW} were plated at a density of 100K cells/well in 96 well plates (Costar). The cells were cultivated for 6 h at 37 ^{o}C and 5% CO_2 in DMEM supplemented with 10% FBS. Cells were incubated overnight with test compounds at concentrations ranging from 0.0005 to 10 μM. Following incubation

with the test compounds the conditioned media was collected and the Aβ40 levels were determined using a sandwich ELISA. The IC_{50} was calculated from the percent of control Aβ40 as a function of the concentration of the test compound. The sandwich ELISA to detect Aβ40 was performed in 96 well microtiter plates, which were pre-coated with goat anti-rabbit IgG (Pierce). The capture and detection antibody pair that was used to detect Aβ40 from cell supernatants consists of affinity purified pAβ40 (Invitrogen) and biotinylated 6E10 (Covance), respectively. Conditioned media was incubated with capture antibody overnight at 4 ºC, followed by washing. The detecting antibody incubation was for 3 h at 4 ^{o}C, again followed by the wash steps as described previously. The plate was developed using Delfia reagents (Streptavidin-Europium and Enhancement solution (Perkin Elmer)) and time-resolved fluorescence was measured on an EnVision multilabel plate reader (Perkin Elmer). The standard deviation and the number of experiments for each compounds are listed in Table 1s.

Permeability assay. The wild type cell line LLC-PK1 (porcine renal epithelial cells, WT-LLC-PK1) was purchased from American Type Culture Collection (ATCC, Manassass, VA). Transfections of WT-LLC-PK1 cells with human *MDR*1 gene (hMDR1-LLC-PK1) and rat *mdr1a* gene (rMdr1a-LLC-PK1) were generated. Cells were grown in Medium 199 supplemented with 10% fetal bovine serum.[iii] Cells were seeded onto matrigel-coated transwell filter membranes at a density of 90,000 cells/well. Media change was performed on day 3. Compound incubations were performed 5-6 days post seeding. All cultures were incubated at 37°C in a humidified (95% relative humidity) atmosphere of 5% CO_2 / 95% air.

Prior to the transport experiment,[iv] culture medium was aspirated from both apical and basolateral wells, cells were rinsed with warmed (37 ^{o}C) Hank's balanced salt solution supplemented with 10 mM Hepes at pH 7.4 (HHBSS, Invitrogen, Grand Island, NY). HHBSS

was removed from wells prior to dosing with test drugs at 5 μM in transport buffer (HHBSS containing 0.1% bovine serum albumin). One hundred-fifty microliters of transport buffer were added to receiver chambers prior to dosing in triplicate to apical or basolateral chambers. The dosed transwell plates containing the cell monolayers were incubated for two hours at 37 °C on a shaking platform. At the end of the incubation period, 100 μl samples were collected from receiver reservoirs, and analyzed by LC-MS/MS on an API4000 (Applied Biosystem, Foster City, CA) triple quadruple mass spectrometer interfaced with turbo IonSpray operated in positive mode using Analyst 1.4.2 software.

The apparent permeability coefficient (P_{app}) of all tested agents was estimated from the slope of a plot of cumulative amount of the agent versus time based on the following equation:

$$P_{app} = (dQ / dt) / (A * C_0)$$

where dQ / dt is the penetration rate of the agent (ng/s), A is the surface area of the cell layer on the Transwell (0.11 cm^2), and C_0 is the initial concentration of the test compound (ng/ml). Efflux ratio (ER) was calculated from the basolateral-to-apical permeability divided by the apical-to-basolateral permeability: $ER = P_{app}$ B>A/ P_{app} A>B.

Microsomal Stability Assay. Compounds (1 μM) were incubated with liver microsomes (0.25 mg/mL in 67 mM phosphate buffer, pH 7.4) from human and rat at 37 °C for 30 min with or without 1 mM NADPH in a total volume of 0.2 mL. The final concentration of DMSO in the incubation was <0.1%. Incubations were stopped by addition of 200 μL of ice-cold acetonitrile containing 0.5% formic acid and an internal standard (500 ng/mL) followed by centrifugation at 3100 rpm for 20 min. The supernatants were analyzed directly (without any further sample cleanup) by high performance liquidchromatography (HPLC) and mass spectrometric detection.

hERG Binding Assay. A stable HEK293 cell line expressing the hERG channel was established in house. Compounds were tested in the [^{3}H]-dofetilide binding assay with cell membranes prepared from this cell line using method of Finlayson with some modifications.[v] Briefly, filtration assays were carried out in 194 μL of binding buffer (10 mM HEPES, pH 7.4, 60 mM KCl, 71.5 mM NaCl, 1 mM $CaCl_2$, 2 mM $MgCl_2$) with 10 μg/well membrane (based on membrane protein) and [^{3}H]-dofetilide (8 nM), 6 μL of compound dissolved in 100% DMSO. Non-specific binding was determined by using 10 μM cold dofetilide (~1000-fold molar excess over hot ligand). The entire assay was conducted in 96-well Whatman® Unifilter plates at room temperature for 90 min. The binding assay was terminated by washing the plates four times on a Millipore® Vacuum filtration manifold with 100 μL/well of ice cold wash buffer (10 mM HEPES, pH 7.4, 131.5 mM NaCl, 1 mM $CaCl_2$, 2 mM $MgCl_2$). The bound radioisotope was quantified using a Packard TopCount® NTS liquid scintillation counter with scintillation fluid.

Rat Pharmacodynamic assay. Male Sprague-Dawley rats (175-200 g) were purchased from Harlan and were maintained on a 12 h light/dark cycle with unrestricted access to food and water until use. Rats were administered compound by oral gavage at the appropriate dose. Rats were euthanized with CO_2 inhalation for 2 min and cisterna magna was quickly exposed by removing the skin and muscle above it. CSF (50-100 μl) was collected with a 30 gauge needle through the dura membrane covering the cisterna magna. Blood was withdrawn by cardiac puncture and plasma obtained by centrifugation for drug exposures. Brains were removed and, along with the CSF, immediately frozen on dry ice and stored at -80 ^oC until use. The frozen brains were subsequently homogenized in 10 volumes of (w/v) of 0.5% Triton X-100 in TBS with protease inhibitors. The homogenates were centrifuged at 100,000 rpm for 30 min at 4 ^oC. The supernatants were analyzed for Aβ40 levels by immunoassay as follows: Meso Scale 96-well

avidin plates were coated with Biotin-4G8 (Covance) and detected with Ruthenium-labeled Fab specific for Aβ40. Plates were read in MSD Sector6000 imager according to manufacturer's recommended protocol (Meso Scale Discovery, Inc.). Aβ40 concentrations were plotted using Graphpad Prism and analyzed by one-way ANOVA followed by Dunnett's multiple comparison analysis to compare drug-treated animals to vehicle-treated controls. Five rats were tested per group, the mean was used to calculate the percentage of aβ lowering and EC_{50}. The conversion percentage is ranged 5-20%.

Monkey Pharmacodynamic assay. Three rhesus monkeys were chronically cathetered in the cisterna magna to allow for serial sampling of CSF in conscious primates without the need for anesthesia. Compound **15** was administered by the oral route at a dose of 5 mg/kg. Serial plasma and CSF samples were taken before dosing to define a baseline and post dose for 168 hours. Plasma and CSF samples where then measured to determine drug concentration by LC/MS, plasma protein binding (by ultracentrifugation) and Aβ by ELISA.

X-ray crystal structure. Recombinant human BACE1 residues 14-453 was over expressed in bacteria as inclusion bodies and refolded using a procedure described by Patel et al.[41] Crystals were grown in similar conditions described in Patel et al.[41] BACE1 protein was concentrated to 8 mg/ml in a buffer containing 20 mM Tris (pH 8.2), 150 mM NaCl, and 1 mM DTT. DMSO (3% v/v) was added to the protein immediately prior to crystallization. Apo crystals of BACE1 were grown at 20 ^{o}C using the hanging drop method/vapor diffusion method, the drops contained 1 μl BACE1 solution and 1 μl reservoir solution. The reservoir solution consisted of 20% (w/v) PEG 5000 monomethylethyl ether (MME), 200 mM sodium citrate (pH 6.6) and 200 mM sodium iodide. Apo BACE1 crystal was soaked overnight in a 5.0 mM compound solution with 33% (w/v) PEG 5000 monomethylethyl ether (MME), 110 mM sodium citrate, 220 mM sodium

iodide and 10 % DMSO (from compound dilution). The following day the crystal was briefly transferred to a cryoprotectant (5.0 mM compound with 33% (w/v) PEG 5000 monomethylethyl ether (MME), 110 mM sodium citrate, 220 mM sodium iodide, 10% DMSO and 22% glycerol) and flash frozen in liquid nitrogen. Data was collected at Advanced Light Source Beamline 5.0.2 (Lawrence Berkeley National Laboratory, Berkeley, CA) at 100 K. Data was processed and scaled using HKL2000.[vi] The crystals belong to the space group $P6_122$ with approximate unit cell dimensions of **a** = **b** = 103 Å, **c** = 169 Å. Molecular replacement was performed using Phaser,[vii] using an apo BACE-1 structure (PDB entry 1w50) as a search model. The structure was refined using Refmac 5,[viii] and the model with ligand was built with Coot.[viii]

Chemistry. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were obtained from Aldrich or EM Science and used directly. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. All microwave assisted reactions were conducted with a Smith synthesizer from Personal Chemistry, Uppsala, Sweden. Silica gel chromatography was performed using either glass columns packed with silica gel (230-400 mesh, EMD Chemicals, Gibbstown, NJ) or prepacked silica gel cartridges (Biotage or ISCO). 1H NMR spectra were recorded on a Bruker 300 MHz or Varian 400 MHz spectrometer at ambient temperature. Chemical shifts are reported in parts per million (ppm, δ units) downfield from tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Purity for final compounds was greater than 95% unless otherwise noted and was measured using Agilent 1100 series high performance liquid chromatography (HPLC) systems with UV detection at 254 nm (system A, Agilent Zorbax Eclipse XDB-C8 4.6 mm × 150 mm, 5

μm, 5 – 100% CH_3CN in H_2O with 0.1% TFA for 15 min at 1.5 mL/min; system B, Waters Xterra 4.6mm × 150 mm, 3.5 μm, 5 – 95% CH_3CN in H_2O with 0.1% TFA for 15 min at 1.0 mL/min). Exact mass confirmation was performed on an Agilent 1100 series high performance liquid chromatography (HPLC) system (Santa Clara, CA, U.S.) by flow injection analysis, eluting with a binary solvent system A and B (A, water with 0.1% FA; B, ACN with 0.1% FA) under isocratic conditions (50% A/ 50% B) at 0.2 mL/min with MS detection by an Agilent G1969A time of flight (TOF) mass spectrometer (Santa Clara, CA, U.S.).

6-Chloro-2-fluoro-3-(methoxymethoxy)pyridine (2s). DIPA (6.0 mL, 42.8 mmol) was dissolved in dry THF (20 mL) and cooled under nitrogen in a dry ice bath. n-Butyllithium solution (2.5 M in hexanes, 17 mL, 42.5 mmol) was added and after stirring for a few minutes a solution of 2-chloro-6-fluoropyridine (5.0 g, 38.0 mmol) in dry THF (20 mL) was added dropwise. The solution was stirred for 50 minutes then a solution of triisopropyl borate (8.72 mL, 38.0 mmol) in dry tetrahydrofuran (10 mL) was added dropwise. The reaction was stirred for 10 minutes. Water (80 mL) was added and the reaction concentrated under reduced pressure until water began to distill. The solution was treated with aqueous sodium hydroxide (10.0 N, 11.40 mL, 114 mmol) and hydrogen peroxide (30% by wt, 4.66 mL, 45.6mmol) and stirred at RT for 90 minutes. Additional hydrogen peroxide (0.75 mL) was added. After stirring for 30 minutes, ice (~100 mL), water (100 mL) and HCl (2N, 60 mL) were added followed by EtOAc (200 ml). The phases were mixed and separated and the organic dried with magnesium sulfate before evaporating to dryness under reduced pressure. The crude intermediate was dissolved in acetone (100 mL) and treated with potassium carbonate (6.30 g, 45.6 mmol) and chloromethyl methyl ether (2.89 mL, 38.0 mmol). The mixture was heated in a 60 °C oil bath and monitored by TLC. The reaction was complete within 2 hours and was concentrated under reduced

pressure to ~ 30 mL. Water (100 mL) and diethyl ether (100 ml) were added and the phases mixed and separated. The organic was dried with magnesium sulfate and evaporated to dryness under reduced pressure. The crude oil was found to be 6-chloro-2-fluoro-3-(methoxymethoxy) pyridine and did not required purification (69% yield for three steps). MS *m/z* = 192.0 $[M+H]^+$. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.55 (dd, *J* = 8.33, 9.65 Hz, 1H), 7.14 (d, *J* = 8.33 Hz, 1H), 5.22 (s, 2H), 3.51 (s, 3H)**.**

(5-Bromo-2-fluorophenyl)(6-chloro-2-fluoro-3-(methoxymethoxy)pyridin-4-yl)methanol (3s). DIPA (0.750 mL, 5.35 mmol) was dissolved in dry THF (20 mL) under nitrogen and cooled in a dry ice bath to -78 °C. Butyllithium solution (2.5 M in hexanes, 2.0 mL, 5.00mmol) was added and the solution was stirred for a few minutes. A solution of 6-chloro-2-fluoro-3-(methoxymethoxy) pyridine (0.864 g, 4.51 mmol) in dry tetrahydrofuran (10 mL) was added slowly and the resulting solution stirred for 40 minutes. A solution of 5-bromo-2-fluorobenzaldehyde (1.02 g, 5.05 mmol) in dry THF (1 mL) was added dropwise. After 10 minutes saturated ammonium chloride (10 mL), water (100 mL) and ethyl acetate (100 mL) were added and the phases mixed and separated. The organic was dried with magnesium sulfate and evaporated to dryness under reduced pressure. Purification using silica chromatography (hexane to ethyl acetate gradient) gave the desired (5-bromo-2-fluorophenyl)(6-chloro-2-fluoro-3-(methoxymethoxy)pyridin-4-yl)methanol (57% yield). MS *m/z* = 395.9 $[M+H]^+$.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.61 (dd, *J*=6.46, 2.54 Hz, 1 H) 7.45 (ddd, *J*=8.71, 4.60, 2.54 Hz, 1 H) 7.15 (s, 1 H) 6.96 (dd, *J*=9.49, 8.90 Hz, 1 H) 6.31 (s, 1 H) 5.09 - 5.21 (m, 2 H) 3.52 (s, 3 H)

7-Bromo-3-chloro-1-fluoro-5H-chromeno[2,3-c]pyridin-5-one (4s). (5-Bromo-2-fluorophenyl)(6-chloro-2-fluoro-3-(methoxymethoxy)pyridin-4-yl)methanol (1.008 g, 2.55

mmol) and 4-methylmorpholine n-oxide (0.898 g, 7.66 mmol) were dissolved in DCM (60 mL) and treated with tetrapropylammonium perruthenate (0.045 g, 0.128 mmol). When the oxidation was complete by TLC (EA / hexane) it was passed through a short silica column using 1:1 EtOAc : DCM to wash off the desired ketone. Evaporation under reduced pressure gave the intermediate as a clear oil that crystallized on standing. It was dissolved in DCM (60 mL) under nitrogen and cooled in an ice bath. Boron tribromide (0.5 mL, 5.29 mmol) was added and the solution turned red. After 5 minutes additional DCM (80 mL) was added followed by ice (~50 mL) and water (100 mL). The phases were mixed and separated and the organic dried with magnesium sulfate before evaporating to dryness under reduced pressure. The crude material was dissolved in dioxane (50 mL) and treated with cesium carbonate (0.246 mL, 3.07 mmol). The reaction was heated to reflux for 30 minutes. It was cooled and water (100 mL) and ethyl acetate (100 mL) were added. The phases were mixed and separated and the organic dried with magnesium sulfate before evaporating to dryness under reduced pressure. The crude product was purified using silica chromatography (hexane to ethyl acetate gradient) to give 7-bromo-3-chloro-1-fluoro-5H-chromeno[2,3-c]pyridin-5-one (69% yield) as a white solid. MS *m/z* = 329.8 $[M+H]^+$.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.45 (d, *J*=2.54 Hz, 1 H) 8.01 (s, 1 H) 7.93 (dd, *J*=8.90, 2.45 Hz, 1 H) 7.54 (d, *J*=9.00 Hz, 1 H)

7-Bromo-3-chloro-1-fluoro-5-methylene-5H-chromeno[2,3-c]pyridine (5s). 7-Bromo-3-chloro-1-fluoro-5H-chromeno[2,3-c]pyridin-5-one (21.5 g, 65.4 mmol) was suspended in dry THF (300 mL) under nitrogen in an ice bath. Methylmagnesium bromide (3.0 M in diethyl ether, 36 mL, 108mmol) was added in ~12 mL portions allowing 10-15 minutes between additions. The mixture was stirred for a 15 minutes after the final addition. Saturated

ammonium chloride (50 mL) was added carefully followed by diethyl ether (200 mL), ethyl aceate (200 mL), water (400 mL) and 2 N HCl (50 mL). The phases were mixed and separated and the organic dried with magnesium sulfate before evaporating to dryness under reduced pressure. The crude alcohol was dissolved in dry THF (300 mL) and treated with HCl (4.0 M solution in 1,4-dioxane, 16 mL, 64.0 mmol). The mixture was heated to 50 °C and stirred for 30 minutes. The crude reaction mixture was evaporated to dryness under reduced pressure. The crude tar was triturated with diethyl ether (200 mL) and stirred in an ice bath. A cream coloured solid precipitated within a few minutes. After 10 minutes the mixture was filtered through a sintered glass frit and dried under high vacuum to give the desired 7-bromo-3-chloro-1-fluoro-5-methylene-5H-chromeno[2,3-c]pyridine (66% yield). MS *m/z* = 327.9 $[M+H]^+$.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.80 (d, *J*=2.35 Hz, 1 H) 7.48 (dd, *J*=8.80, 2.15 Hz, 1 H) 7.44 (s, 1 H) 7.11 (d, *J*=8.80 Hz, 1 H) 5.75 (d, *J*=1.17 Hz, 1 H) 5.69 (d, *J*=1.37 Hz, 1 H)

(S)-7-Bromo-3-chloro-1-fluoro-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (6s). 7-Bromo-3-chloro-1-fluoro-5-methylene-5H-chromeno[2,3-c]pyridine (14.2 g, 43.5 mmol) was dissolved in dry THF (400 mL) under nitrogen and cooled in an ice bath. Silver cyanate (19.55 g, 130 mmol) was added followed by slow addition of a solution of iodine (11.04 g, 43.5 mmol) in dry tetrahydrofuran (80 mL) over 30 minutes. It was stirred for another 30 minutes then it was filtered through a pad of celite. The filtrate was treated with ammonia (2.0 M solution in methanol, 250 mL, 500mmol) and capped. The solution was stirred for 10 hours. The crude reaction was concentrated under reduced pressure to ~100 mL then diluted with DCM (300 mL). The solution was washed with aqueous sodium sulfite to remove iodine then evaporated to dryness under reduced pressure. DCM/MeOH (60:40, 300 mL) were added to the solids and the crude was triturated for 10 minutes before filtering through a pad of celite. The

solution was evaporated to dryness under reduced pressure to give 7-bromo-3-chloro-1-fluoro-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine. Racemic material was separated by SFC on Chiralpak AY column using acetonitrile/methanol (9:1 + 0.1% triethylamine). The R-enantiomer was eluted as the first peak and the S-enantiomer was eluted as the second peak (40% yield for the S-enantiomer after the purification). MS *m/z* = 383.8 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.58 (dd, *J*=8.71, 2.45 Hz, 1 H) 7.44 (d, *J*=2.54 Hz, 1 H) 7.28 (d, *J*=8.80 Hz, 1 H) 7.25 (s, 1 H) 6.71 (s, 2 H) 4.32 (d, *J*=9.00 Hz, 1 H) 4.21 (d, *J*=9.00 Hz, 1 H)

(S)-3-chloro-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (7s). A mixture of (S)-7-bromo-3-chloro-1-fluoro-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (40.0 mg, 0.104 mmol), pyridin-3-ylboronic acid (21.73 mg, 0.177 mmol), bis-(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(ii) (2.95 mg, 4.16 μmol) and potassium phosphate (66.2 mg, 0.312 mmol) in 1.5 ml of dioxane/water = 2:1 was heated at 120 ^{o}C microwave for 20 min. LCMS showed mostly conversion to the mono coupling product. 10 mg of pyridin-3-ylboronic acid (21.73 mg, 0.177 mmol) was added and the reaction was heated at 140 ^{o}C under microwave for 20 min. The reaction mixture was directly loaded to column chromatography (SiO2, DCM to DCM/MeOH = 100:1 to 100:6) to give crude final product which was further purified by prep TLC (DCM/MeOH) to give 1-fluoro-3,7-di(pyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine as a white solid. MS *m/z* = (M+1): 401.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.25 (dt, *J*=4.69, 1.60 Hz, 1 H) 8.12 (ddd, *J*=10.07, 7.73, 1.76 Hz, 1 H) 7.65 (dt, *J*=8.61, 1.60 Hz, 1 H) 7.58 (t, *J*=1.60 Hz, 1 H) 7.49 (ddd, *J*=7.09, 5.04,

1.76 Hz, 1 H) 7.42 (d, *J*=8.41 Hz, 1 H) 7.25 (s, 1 H) 6.69 (s, 2 H) 4.38 (d, *J*=8.80 Hz, 1 H) 4.24 (d, *J*=8.80 Hz, 1 H)

(S)-1-Fluoro-7-(2-fluoropyridin-3-yl)-3-phenyl-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (5). The titled compound was synthesized by procedure analogous to that described in compound **15** below, but using phenylbronic acid. MS *m/z* = 442.8 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.34 (d, *J*=8.8 Hz, 1 H), 4.46 (d, *J*=8.8 Hz, 1 H), 6.62 (s, 2 H), 7.41 - 7.56 (m, 5 H), 7.62 (d, *J*=1.7 Hz, 1 H), 7.64 - 7.69 (m, 1 H), 7.73 (s, 1 H), 7.94 - 7.99 (m, 2 H), 8.14 (ddd, *J*=10.3, 7.5, 1.9 Hz, 1 H), 8.24 - 8.28 (m, 1 H).

(S)-1-Fluoro-7-(2-fluoropyridin-3-yl)-3-(pyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (6). The titled compound was synthesized by procedure analogous to that described in compound **15** below, but using 3-pyridylboronic acid. MS *m/z* = 444.0 $[M+H]^+$.

^{1}H NMR (400MHz ,MeOH) δ = 9.49 (d, *J* = 1.2 Hz, 1 H), 9.10 (d, *J* = 8.2 Hz, 1 H), 8.84 (d, *J* = 5.1 Hz, 1 H), 8.43 (s, 1 H), 8.26 (d, *J* = 4.7 Hz, 1 H), 8.17 (ddd, *J* = 1.8, 7.7, 9.7 Hz, 1 H), 8.04 (dd, *J* = 5.5, 8.0 Hz, 1 H), 7.89 (s, 1 H), 7.85 (d, *J* = 8.8 Hz, 1 H), 7.56 (d, *J* = 8.6 Hz, 1 H), 7.51 - 7.44 (m, 1 H), 5.25 (s, 2 H)

(S)-1-Fluoro-7-(2-fluoropyridin-3-yl)-3-(pyridin-4-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (7). The titled compound was synthesized by procedure analogous to that described in compound **15** below, but using 4-pyridylboronic acid. MS *m/z* = 443.9 $[M+H]^+$.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.70 (d, *J*=6.06 Hz, 2H), 8.20 (d, *J*=4.89 Hz, 1H), 7.82-7.91 (m, 3H), 7.74 (s, 1H), 7.66 (s, 1H), 7.57 (d, *J*=8.61 Hz, 1H), 7.37 (d, *J*=8.61 Hz, 1H), 7.29 (dd, *J*=1.76, 7.04 Hz, 1H), 4.43 (q, *J*=8.67 Hz, 2H)

(5S)-1-Fluoro-7-(2-fluoropyridin-3-yl)-3-(6-methylpyridin-3-yl)spiro[chromeno[2,3-c]pyridine-5-4'-[1,3]oxazol]-2'-amine (8). The titled compound was synthesized by procedure analogous to that described in compound **15** below, but using 2-methyl-pyridin-5-ylboronic acid. MS *m*/*z* = 458.1 $[M+H]^+$.

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.60 (s, 3 H) 4.40 (s, 2 H) 7.19-7.26 (m, 2 H) 7.34 (d, J=8.4 Hz, 1 H) 7.52-7.57 (m, 1 H) 7.62-7.67 (m, 2 H) 7.83-7.89 (m, 1 H) 8.10-8.18 (m, 2 H) 9.02 (d, J=1.8 Hz, 1 H).

(S)-1-Fluoro-7-(2-fluoropyridin-3-yl)-3-(2-methylpyridin-4-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (9). The titled compound was synthesized by procedure analogous to that described in compound **15** below, but using (2-methylpyridin-4-yl)boronic acid. MS *m*/*z* = 458.0 $[M+H]^+$.

^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 2.49 (s, 3 H) 4.39 (d, *J*=9.00 Hz, 1 H) 4.43 (d, *J*=9.00 Hz, 1 H) 4.73 (br. s., 2 H) 7.25 (d, *J*=8.41 Hz, 1 H) 7.31 (ddd, *J*=7.19, 5.14, 1.56 Hz, 1 H) 7.52 (dt, *J*=8.61, 1.40 Hz, 1 H) 7.59 (t, *J*=1.80 Hz, 1 H) 7.67 (dd, *J*=5.28, 0.98 Hz, 1 H) 7.75 (s, 1 H) 7.80 (s, 1 H) 7.95 (ddd, *J*=9.83, 7.68, 1.86 Hz, 1 H) 8.08 (d, *J*=4.70 Hz, 1 H) 8.36 (d, *J*=5.28 Hz, 1 H)

(S)-1-Fluoro-3,7-bis(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (10). The titled compound was synthesized by procedure analogous to that described in compound **15** below, but using (2-fluoropyridin-3-yl)boronic acid. MS *m*/*z* = 462.0 $[M+H]^+$.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.46-8.62 (m, 1H), 8.22 (dd, *J*=4.69, 9.59 Hz, 2H), 7.96 (t, *J*=8.51 Hz, 1H), 7.89 (s, 1H), 7.67 (s, 1H), 7.61 (d, *J*=8.61 Hz, 1H), 7.35-7.45 (m, 3H), 4.42-4.54 (m, 2H)

(S)-1-Fluoro-7-(2-fluoropyridin-3-yl)-3-(6-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (11). The titled compound was synthesized by procedure analogous to that described in compound **15** below, but using (6-fluoropyridin-3-yl)boronic acid. MS *m*/*z* = 462.0 $[M+H]^+$.

^{1}H NMR (400 MHz, Solvent) δ ppm 3.21 (dt, *J*=3.28, 1.59 Hz, 3 H) 4.41 (d, *J*=9.00 Hz, 1 H) 4.44 (d, *J*=9.00 Hz, 1 H) 4.75 (br s, 2 H) 7.20 - 7.37 (m, 2 H) 7.46 - 7.59 (m, 2 H) 7.60 (s, 1 H) 7.77 - 7.84 (m, 1 H) 7.87 (s, 1 H) 7.98 (ddd, *J*=9.88, 7.63, 1.86 Hz, 1 H) 8.10 (d, *J*=4.50 Hz, 1 H) 8.19 (d, *J*=5.28 Hz, 1 H)

(S)-1-Fluoro-7-(2-fluoropyridin-3-yl)-3-(2-fluoropyridin-4-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (12). The titled compound was synthesized by procedure analogous to that described in compound **15** below, but using (2-fluoropyridin-4-yl)boronic acid. MS *m*/*z* = 462.0 $[M+H]^+$.

^{1}H NMR (400 MHz, Solvent) δ ppm 3.21 (dt, *J*=3.28, 1.59 Hz, 3 H) 4.41 (d, *J*=9.00 Hz, 1 H) 4.44 (d, *J*=9.00 Hz, 1 H) 4.75 (br s, 2 H) 7.20 - 7.37 (m, 2 H) 7.46 - 7.59 (m, 2 H) 7.60 (s, 1 H) 7.77 - 7.84 (m, 1 H) 7.87 (s, 1 H) 7.98 (ddd, *J*=9.88, 7.63, 1.86 Hz, 1 H) 8.10 (d, *J*=4.50 Hz, 1 H) 8.19 (d, *J*=5.28 Hz, 1 H)

(S)-3-(3,4-Dihydro-2H-pyran-5-yl)-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (13). The titled compound was

synthesized by procedure analogous to that described in compound **15** below, but using 2-(3,4-dihydro-2H-pyran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. MS *m/z* = 448.8 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.26 (ddd, *J*=1.4, 1.6, 8.8 Hz, 1H), 8.12 (ddd, *J*=1.9, 7.5, 10.3 Hz, 1H), 7.63 (ddd, *J*=1.6, 1.7, 8.8 Hz, 1H), 7.60 - 7.56 (m, 1H), 7.53 - 7.45 (m, 2H), 7.38 (d, *J*=8.5 Hz, 1H), 7.03 (s, 1H), 6.61 (br. s., 2H), 4.35 (d, *J*=8.4 Hz, 1H), 4.27 (d, *J*=8.4 Hz, 1H), 4.02 (t, *J*=5.2 Hz, 2H), 2.45 - 2.20 (m, 2H), 2.02 - 1.85 (m, 2H). MS (ESI) *m/z* 448.8 (M+H).

(S)-3-(3,4-Dihydro-2H-pyran-6-yl)-1-fluoro-7-(2-fluoropyridin-3-yl)-5'-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (14). The titled compound was synthesized by procedure analogous to that described in compound **15** below, but using 2-(3,4-dihydro-2H-pyran-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. MS *m/z* = 449.0 $[M+H]^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.19 (d, *J*=4.70 Hz, 1H), 7.87 (ddd, *J*=1.86, 7.58, 9.73 Hz, 1H), 7.60 (s, 1H), 7.53 (d, *J*=8.61 Hz, 1H), 7.44 (s, 1H), 7.30 (d, *J*=8.61 Hz, 1H), 7.27-7.28 (m, 1H), 5.96 (t, *J*=4.11 Hz, 1H), 4.37-4.48 (m, 2H), 4.10-4.25 (m, 2H), 2.20-2.29 (m, 2H), 1.92 (td, *J*=5.84, 11.20 Hz, 2H)

(S)-3-(5,6-dihydro-2H-pyran-3-yl)-1-fluoro-7-(3-fluoropyridin-2-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (15). A 20 mL glass microwave reaction vessel was charged with (S)-3-chloro-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (0.975 g, 2.433 mmol), potassium phosphate (1.136 g, 5.35 mmol), 2-(5,6-dihydro-2H-pyran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.022 g, 4.87 mmol) and bis-(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (0.086 g, 0.122 mmol) in 15 mL dioxane and water (2:1). The reaction mixture was stirred and heated at 135 °C for 25 min in microwave reactor. The mixture was diluted with EtOAc and water. The organic layer was washed twice

with saturated Na_2CO_3, dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by two column chromatography with 25-100% dichloromethane/EtOAc first, then 2-6% MeOH/dichloromethane to give the desired product (665 mg, 61% yield)s. MS m/z = 449.10 $[M+H]^+$.

^{1}H NMR (500 MHz, DMSO-*d*6) δ ppm 2.24 - 2.35 (m, 2 H) 3.67-3.81 (m, 2 H) 4.26-4.38 (dd, 2 H) 4.39 - 4.53 (m, 2 H) 6.57 - 6.65 (m, 2 H) 6.67-6.75 (m, 1 H) 7.28 (s, 1 H) 7.36 - 7.44 (m, 1 H) 7.46-7.54 (m, 1 H) 7.58 (s, 1 H) 7.61 - 7.68 (m, 1 H) 8.08-8.17 (m, 1 H) 8.21 - 8.33 (m, 1 H)

^{13}C NMR (101 MHz, DMSO-*d*6) δ ppm 163.2, 160.6, 158.3, 148.6, 148.6, 146.5, 146.4, 145.9, 145.8, 141.1, 141.1, 141.1, 141.1, 140.0, 133.6, 131.9,131.7, 129.8, 129.8, 129.7, 129.5, 127.9, 127.9, 127.9, 126.4, 125.0, 122.7, 122.7, 122.7, 122.2, 121.9, 116.8, 113.8, 113.8, 113.8, 82.4, 66.0, 66.0,66.0, 64.8, 63.1, 25.0

(S)-3-(3,6-Dihydro-2H-pyran-4-yl)-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (16). A reaction vessel charged with (S)-3-chloro-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (95 mg, 0.237 mmol; **11**) 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (100 mg, 0.474 mmol), bis-(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (8.39 mg, 0.012 mmol) and potassium phosphate (111 mg, 0.522 mmol) in 1.5 ml of a 2:1 mixture of dioxane and was heated at 135 °C microwave for 25 minutes. The reaction mixture was loaded directly onto a silica gel column and purified (CH_2Cl_2 to CH_2Cl_2/ethyl acetate = 3:1 to 2:1 to 1:1 to 100% ethyl acetate to ethyl acetate/MeOH = 100:5) to provide (S)-3-(3,6-dihydro-2H-pyran-4-yl)-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine as a off-white solid. MS *m/z* = 449.0 $[M+H]^+$.

^{1}H NMR (400MHz ,CHLOROFORM-d) δ = 8.18 (d, *J* = 4.7 Hz, 1 H), 7.87 (ddd, *J* = 1.8, 7.7, 9.7 Hz, 1 H), 7.64 (s, 1 H), 7.53 (d, *J* = 8.6 Hz, 1 H), 7.33 (d, *J* = 8.6 Hz, 1 H), 7.30 - 7.25 (m, 1 H), 7.22 (s, 1 H), 6.68 (br. s., 1 H), 4.47 - 4.29 (m, 4 H), 3.92 (t, *J* = 5.5 Hz, 2 H), 2.56 (d, *J* = 2.2 Hz, 2 H)

(4'S)-1-Fluoro-7-(2-fluoropyridin-3-yl)-3-(tetrahydro-2H-pyran-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (17). (S)-3-(5,6-dihydro-2H-pyran-3-yl)-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (0.295 g, 0.658 mmol, **22**) was dissolved in EtOH 5 mL and palladium, 10% wt. on activated carbon (0.070 g, 0.658 mmol) was added. The reaction was stirred at room temperature under a hydrogen balloon overnight. The mixture was filtered through a pad of celite. The filtrate was concentrated and purified by column chromatography with 2.5-5.5 % MeOH in dichloromethane. The pure fractions were collected and concentrated to give 0.103 g of desired product. The frations with impurities were collected and purified by prep-TLC plate with 5% 2M NH3 in MeOH/diethyl ether to give 0.1441 g of additional desired product. MS *m/z* = 451.1 $[M+H]^+$.

(S)-1-Fluoro-7-(2-fluoropyridin-3-yl)-3-(tetrahydro-2H-pyran-4-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (18). A suspension of (S)-3-(3,6-dihydro-2H-pyran-4-yl)-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (60 mg, 0.134 mmol; **23**) and 10% Pd/C (60 mg) was stirred at rt under 1 atm of H_2 gas for 12 hours. The suspension was filtered through a pad of silica gel washing with a 1:1 mixture of CH_2Cl_2 /MeOH. The filtrate was evaporated to dryness and purified by silica gel chromatography (EtOAc to EtOAc/MeOH = 100:5 to 100:7) to provide (S)-1-fluoro-7-(2-fluoropyridin-3-yl)-3-(tetrahydro-2H-pyran-4-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine as an off-white solid. MS *m/z* = 451.0 $[M+H]^+$.

^{1}H NMR (400MHz ,CHLOROFORM-d) δ = 8.18 (d, *J* = 4.7 Hz, 1 H), 7.87 (ddd, *J* = 1.9, 7.6, 9.7 Hz, 1 H), 7.63 (t, *J* = 1.7 Hz, 1 H), 7.54 (d, *J* = 8.4 Hz, 1 H), 7.32 (d, *J* = 8.4 Hz, 1 H), 7.30 - 7.24 (m, 1 H), 7.08 (s, 1 H), 4.44 - 4.32 (m, 2 H), 4.11 - 4.05 (m, 2 H), 3.52 (dt, *J* = 3.0, 11.4 Hz, 2 H), 2.95 - 2.82 (m, 1 H), 1.94 - 1.81 (m, 4 H), 1.99 - 1.80 (m, 4 H)

(5S)-1-Fluoro-7-(2-fluoro-3-pyridinyl)-3-(4-morpholinyl)spiro[chromeno[2,3-c]pyridine-5,4'-[1,3]oxazol]-2'-amine (19). The titled compound was synthesized by steps analogous to those described in compound **20** below but using morpholine. MS *m/z* = 452.1 $[M+H]^+$.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm, 3.44 (m, 4 H), 3.82 (m, 4 H), 4.34 (s, 2 H), 6.44 (s, 1 H), 7.24 - 7.32 (m, 1 H), 7.49 - 7.55 (m, 1 H), 7.61 (br. s., 1 H), 7.83 - 7.91 (m, 1 H), 8.17 (br. s., 1 H), 8.17 - 8.21 (m, 1 H). 8.26 (m, 1 H)

(S)-3-(4,4-Difluoropiperidin-1-yl)-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (20). In a sealed tube a mixture of (S)-3-bromo-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (0.095 g, 0.213 mmol), 4,4-difluoropiperidine hydrochloride (0.040 g, 0.256 mmol), and Chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]Pd(II) Me-*t*-butylether (0.016 g, 0.021 mmol), was purged with N_2 followed by the addition of dioxane (1 mL) and lithium bis(trimethylsilyl)amide (0.768 mL, 0.768 mmol) and the resulting mixture was stirred at rt for 2 h. The mixture was quenched with sat NH_4Cl and extracted with EtOAc. The combined organics were dried over Na_2SO_4, filtered, concentrated, and purified by HPLC to afford an off-white solid as (S)-3-(4,4-difluoropiperidin-1-yl)-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (0.0287 g, 0.059 mmol, 27.7 % yield). MS *m/z* = 486.1 $[M+H]^+$.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.93 – 2.12 (m, 4 H) 3.58 – 3.70 (m, 4 H) 4.32 (s, 2 H) 6.50 (s, 1 H) 7.20 – 7.32 (m, 2 H) 7.51 (dt, *J*=8.48, 1.83 Hz, 1 H) 7.62 (t, *J*=1.83 Hz, 1 H) 7.85 (ddd, *J*=9.79, 7.60, 1.90 Hz, 1 H) 8.15 (dt, *J*=4.71, 1.52 Hz, 1 H).

(S)-3-(3,3-difluoropyrrolidin-1-yl)-1-fluoro-7-(2-fluoropyridin-3-yl)-5'-*H*-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (21). In a sealed tube a mixture of (S)-3-bromo-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (0.71 g, 1.595 mmol), 3,3-difluoropyrrolidine hydrochloride (0.229 g, 1.595 mmol), and Chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]Pd(II) Me-*t*-butylether (0.118 g, 0.159 mmol), was purged with N_2 followed by the addition of dioxane (1 mL) and lithium bis(trimethylsilyl)amide (3.19 mL, 3.19 mmol) and the resulting mixture was stirred at rt for 3 h. The reaction mixture was quenched with sat NH_4Cl and extracted with EtOAc. The combined organics were dried over Na_2SO_4, filtered, concentrated, and purified by HPLC to afford a white solid as (S)-3-(3,3-difluoropyrrolidin-1-yl)-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (0.085 g, 0.180 mmol, 11.31 % yield). MS *m/z* = 472.1 $[M+H]^+$.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.48 (tt, *J*=13.78, 6.98 Hz, 2 H) 3.66 (t, *J*=7.23 Hz, 2 H) 3.81 (t, *J*=13.08 Hz, 2 H) 4.27 - 4.38 (m, 2 H) 6.16 (s, 1 H) 7.21 - 7.33 (m, 2 H) 7.51 (d, *J*=8.48 Hz, 1 H) 7.61 (s, 1 H) 7.86 (ddd, *J*=9.72, 7.60, 1.83 Hz, 1 H) 8.17 (d, *J*=4.68 Hz, 1 H).

(S)-1-Fluoro-7-(2-fluoropyridin-3-yl)-3-((R)-3-fluoropyrrolidin-1-yl)-5'-*H*-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (22). In a sealed tube a mixture of (S)-3-bromo-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (0.71 g, 1.595 mmol), 3,3-difluoropyrrolidine hydrochloride (0.229 g, 1.595 mmol), and Chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-

aminoethyl)phenyl]Pd(II) Me-t-butylether (0.118 g, 0.159 mmol), was purged with N_2 followed by the addition of dioxane (1 mL) and lithium bis(trimethylsilyl)amide (3.19 mL, 3.19 mmol) and the resulting mixture was stirred at rt for 3 h. The reaction mixture was quenched with sat NH_4Cl and extracted with EtOAc. The combined organics were dried over Na_2SO_4, filtered, concentrated, and purified by HPLC to afford a white solid as (S)-3-(3,3-difluoropyrrolidin-1-yl)-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (0.085 g, 0.180 mmol, 11.31 % yield). MS *m/z* = 454.0 $[M+H]^+$.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.93 - 2.49 (m, 2 H) 3.43 - 3.98 (m, 4 H) 4.21 - 4.46 (m, 2 H) 5.28 (d, *J*=10.38 Hz, 1 H) 6.17 (s, 1 H) 7.16 - 7.39 (m, 3 H) 7.43 - 7.56 (m, 1 H) 7.51 (d, *J*=8.62 Hz, 1 H) 7.61 (s, 1 H) 7.77 - 7.96 (m, 1 H) 8.17 (d, *J*=4.53 Hz, 1 H).

(S)-1-Fluoro-7-(2-fluoropyridin-3-yl)-3-(3-methylisoxazol-5-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (23). To a microwave tube, was added (S)-3-chloro-1-fluoro-7-(2-fluoropyridin-3-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine (0.28 g, 0.699 mmol), 3-methyl-5-(tributylstannyl)isoxazole (0.78 g, 2.096 mmol), AMPhos (0.148 g, 0.210 mmol) and 9 mL of dioxane. The reaction mixture was heated at 110 ^oC for 1 h and cooled. The mixture was diluted with DCM (2 mL) and injected directly to a reversed phase HPLC. The pure fractions were collected, added sodium carbonate (10%, 50 mL) , and extracted with EtOAc twice. The combined organic layers were washed with brine, dried on sodium sulfate, filtered and concentrated to give (S)-1-fluoro-7-(2-fluoropyridin-3-yl)-3-(3-methylisoxazol-5-yl)-5'H-spiro[chromeno[2,3-c]pyridine-5,4'-oxazol]-2'-amine as a pale yellow oil (0.034 g, 0.040 mmol, 5.8% yield). MS *m/z* = 448.0 $[M+H]^+$.

[1]H NMR (300 MHz, CHLOROFORM-*d*) δ ppm δ 8.21 (d, *J*=4.95 Hz, 1H), 7.78-7.91 (m, 2H), 7.64 (s, 1H), 7.58 (d, *J*=7.97 Hz, 1H), 7.24-7.36 (m, 3H), 6.66 (s, 1H), 4.38-4.51 (m, 2H), 2.38 (s, 3H)

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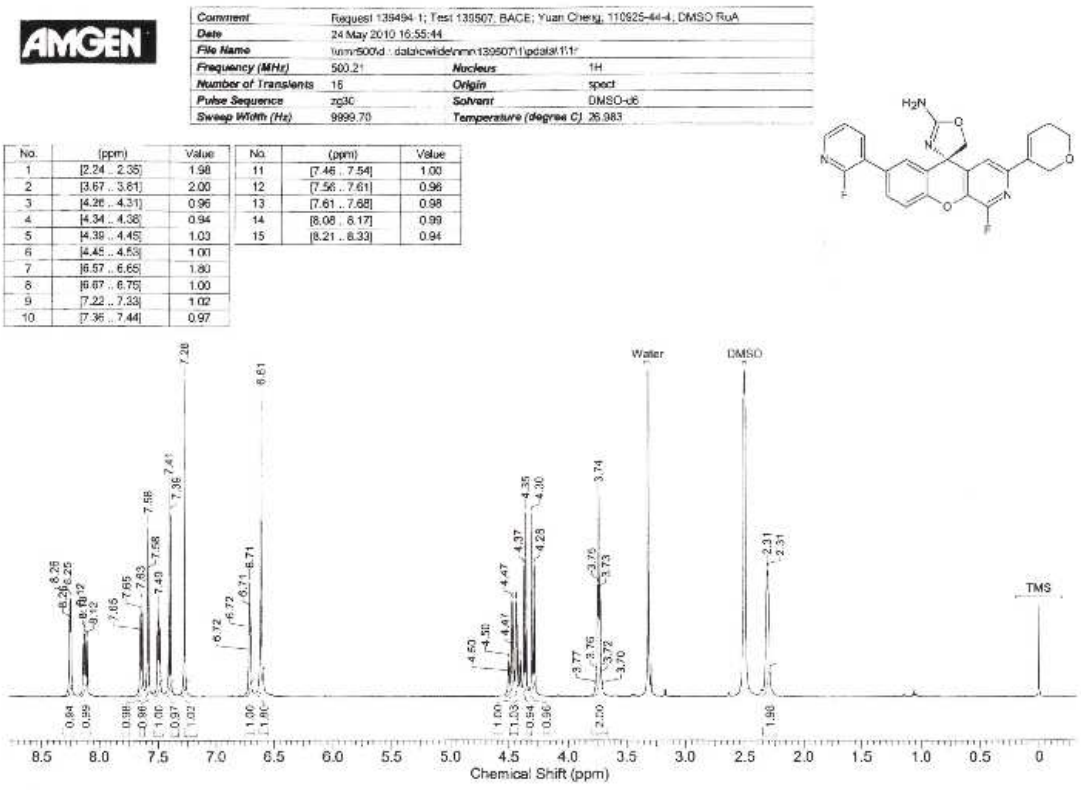
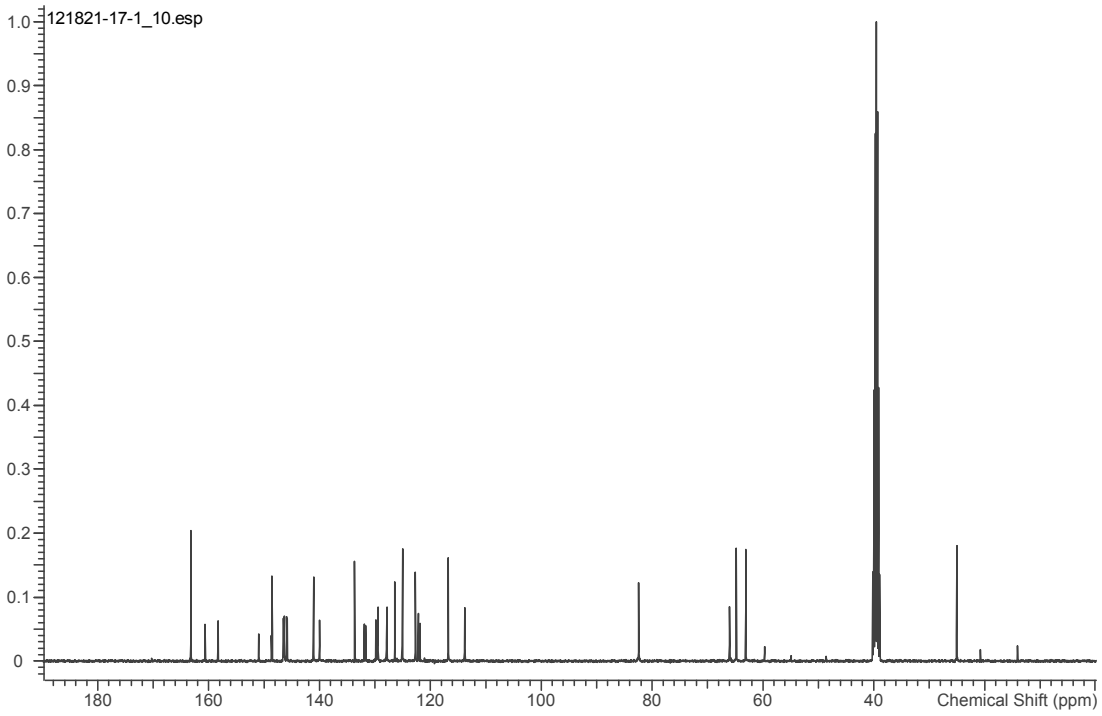
^{1}H NMR and ^{13}C NMR spectra of Compound 15



No.	(ppm)	Value
1	[2.24 .. 2.35]	1.98
2	[3.67 .. 3.81]	2.00
3	[4.26 .. 4.31]	0.96
4	[4.34 .. 4.38]	0.94
5	[4.39 .. 4.45]	1.03
6	[4.45 .. 4.53]	1.00
7	[6.57 .. 6.65]	1.80
8	[6.67 .. 6.75]	1.00
9	[7.22 .. 7.33]	1.02
10	[7.36 .. 7.44]	0.97

No.	(ppm)	Value
11	[7.46 .. 7.54]	1.00
12	[7.56 .. 7.61]	0.96
13	[7.61 .. 7.68]	0.98
14	[8.08 .. 8.17]	0.99
15	[8.21 .. 8.33]	0.94


121821-17-1_10.esp
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
180
160
140
120
100
80
60
40
Chemical Shift (ppm)